

1995 MINUTES
PERINATAL HAEMOSTASIS SUBCOMMITTEE

Saturday, 10 June, 1995, 8:00-12:00

Chair: M. Andrew (Canada)

Co-Chairpersons: *J. Bonnar (UK); M. Hellgren (Sweden) *Absent

I. Vitamin K Deficiency

1. Introduction and report on the vitamin K international symposium by Dr. T. Sutor (Germany). Unfortunately, several presenters did not arrive. However, the extra time was effectively used for a full subcommittee discussion on recommendations to be included in an official publication from ISTH. Issues discussed were: terminology, definition, diagnosis, classification, prophylaxis.

II. Coagulation Protein Concentrates

Homozygous Protein C Deficiency

1. Ms. L. Mitchell (Canada) presented data on the subcutaneous administration of protein C in rabbits. Survival of protein C in an active form was observed for 77 hours.
2. Dr. M. David (Canada) reported on the successful subcutaneous administration of protein C concentrate in a young child for 48 hours.
3. Dr. P. Shwartz (Austria) updated the subcommittee on the intravenous use of protein C concentrate worldwide.
4. A presentation of the questions regarding dosage, response, pharmacokinetics, and risks of the use of coagulation protein concentrates in newborns was given by Dr. M. Dreyfus (France). There was general support from the subcommittee for the establishment of a registry.

III. International Trials in Perinatal Haemostasis

1. A brief summary of childhood thrombophilia was given by M. Andrew (Canada). There was agreement that the name of the subcommittee should be changed to Perinatal/Pediatric Subcommittee. Enormous interest was expressed by the audience. There was agreement that international studies in the prevention and treatment of thrombotic disease were needed and could be facilitated by the subcommittee.

2. A summary on the use of estrogen in women was given by Dr. J. Deuketis (Canada). The discussion focused on the need for clinical trials but that they may not be feasible (legally) in some countries.

IV. Mini Reports

1. Dr. Suzuki (Japan) reported on the use of the thrombostat 4000 in evaluating prethrombostat effects of pregnancy and oestrogen use.

2. Dr. C. Kaplan (France) reported on the treatment of the fetus with allo-immune thrombocytopenia. The need for individual clinicians to collaborate on studies addressing optimal treatment was accepted by the subcommittee.

1996 MINUTES

PERINATAL/PEDIATRIC HEMOSTASIS SUBCOMMITTEE

Sunday, 23 June, 1996, 13.00 - 17.00

Room Vivaldi, Fira Palace Hotel

Barcelona, Spain

Chair: M. Andrew, Canada

Co-Chairs: R. von Kries, Germany; M. Hellgren, Sweden;

M. Manco-Johnson, USA; A. Sutor, Germany

The agenda of the meeting was constructed with the assistance of all members of the subcommittee who were contacted in December 1995 for their suggestions. Due to the inability of Dr. Helgren to attend the 1996 subcommittee, topics that were specifically perinatal were deferred until 1997. The final agenda contained two parts; presentations on thromboembolic disease in the infant and child, and secondly on recommendations for prophylactic use of vitamin K in newborns.

Dr. Andrew introduced the topics focused on thromboembolic disease in children by summarizing the activities of the subcommittee on this problem over the past year. There was joint sponsorship of an International Children's Thrombophilia Network by the subcommittee and the Canadian Children's Thrombophilia Society. Dr. Andrew reported on the membership and accomplishments of the Network. Approximately 250 institutions world wide are part of the network. Any physician interested in the field can join the Network. A quarterly newsletter and relevant new publications in the literature are regularly mailed to the membership. Educational pamphlets on the use of oral anticoagulants, heparin and thrombolytic agents were prepared over the year and provided to the Network. Two international randomized controlled trials were funded by industry and will assess the role of low molecular weight heparin in pediatric patients.

Pediatric Thromboembolic Disease: The first presentation was by Dr. Nowak-Gottl who presented the results of a registry in Germany on thromboembolic complications in newborns. Several important issues were identified and discussed including the underlying diseases, importance of vascular catheters as insiting agents for arterial and venous thrombosis, the difficulties in performing angiographic studies in newborns and reliance on doppler/ultrasound, the presence of congenital prothrombotic disorders, and the rather inconsistent use of antithrombotic agents for both the specific agent, and duration of therapy. The discussion focused on the difficult issue of treatment, particularly the lack of information on the indications for long-term treatment. In addition, the uncertainty of the optimal way of managing children with congenital prothrombotic disorders was assessed and discussed. The second presentation was by L. Mitchell who presented a Canadian cross sectional study assessing the relationship between antiphospholipid antibodies (APLA) and thromboembolic events in children with systemic lupus erythematosus (SLE). The results clearly showed that the persistent presence of APLA are highly predictive of thrombotic events in children with SLE. The discussion focused on the short term and long-term treatment of these children with anticoagulants.

The third presentation was Dr. M. Manco-Johnson who presented case series describing the presence of APLA in a variety of childhood conditions, particularly ivaricella. She presented data describing the co-existence of acquired protein S and C deficiency. The fourth presentation was Dr. Michelle David who reviewed the world literature and the Canadian registry of children with mechanical heart valves. The Canadian registry contained approximately 100 children followed for approximately 10,000 patient years. Together the data showed that the incidence of thrombotic events was low if adequate therapy with oral anticoagulants were used. The data did not support the routine use of an antiplatelet agent but the latter strategy could be used for children who had had events while receiving adequate treatment with oral anticoagulants. There was agreement from the subcommittee that Dr. David should prepare a position paper for publication as recommendations from the ISTH on the management of children with mechanical heart valves. The fifth presentation was by Dr. N. Schlegle and focused on the mechanisms responsible for thrombotic complications in children with nephrotic syndrome. The final presentation was by Dr. A. Michelson who provided a summary of the recently published North American guidelines for antithrombotic therapy in children. Each of the recommendations was presented in detail and the subcommittee agreed to ask Dr. Michelson to prepare a position paper for publication as recommendations from the

ISTH. Discussions for all presentations identified the urgent need for clinical trials with the goal of assessing the optimal use of antithrombotic agents in children. The need for concurrent studies assessing the relationship of congenital prothrombotic disorders to the development of thrombotic complications in children was also discussed.

Vitamin K Deficiency: Drs. von Kries and Sutor chaired this portion of the program. The position paper prepared by Dr. Sutor based on discussions at the subcommittee in 1995 was presented. The manuscript had been circulated to the entire subcommittee within the previous two months and their comments incorporated into the manuscript. There remained two problematic areas, the merits of frequent low dose vitamin K supplementation in the postnatal period compared to the use of high dose intramuscular injection and the relationship between Vitamin K supplementation and childhood cancer. Dr. M. Cornelissen presented new information on daily low dose vitamin K supplementation and Dr. Von Kries discussed the literature and his own comprehensive study describing the relationship between vitamin K deficiency and cancer. There was agreement from the subcommittee that Dr. Sutor should form a working group to finalize a position paper for publication as recommendations from the ISTH.

There was a final informal discussion of the two funded international trials assessing the role of LMWH in children with thrombotic disease. Other problems that required clinical trials to answer the questions were discussed. The plan was for frequent communications of protocols over the upcoming year and to plan for a meeting at the American Society Of Hematology in approximately 6 months.

1997 MINUTES

PERINATAL/PEDIATRIC HEMOSTASIS

Saturday, 7 June, 1997, 8:00-12:00

Giotto II, Fortezza da Basso

Florence, Italy

Chair: M. Manco-Johnson, USA

**Co-Chairs: M. Andrew, Canada; M. Hellgren, Sweden; R. von Kries, Germany;
A. Sutor, Germany**

1. Neonatal Alloimmune Thrombocytopenia

Dr. Jim Bussell, USA, presented recommendations regarding which infants should be evaluated for NAIT and which laboratory assays are appropriate to assign the diagnosis. The recommendations incorporate platelet count, family history and clinical assessment of the infant. Testing will consider the racial and ethnic background of the parents. The subcommittee agreed that the recommendations be adopted as suggested by Dr. Bussell and further recommended publication in a pediatric journal as the targeted audience includes neonatologists and general pediatricians.

2. Idiopathic Thrombocytopenia Purpura

Dr. Antony Sutor, Germany, discussed the diagnosis of childhood ITP with emphasis upon inaccuracy in automated methods for platelet counting and pitfalls in assignment of diagnosis based solely upon platelet count. In order to evaluate the recent American Society of Hematology clinical practice guidelines for ITP, it was decided that data is needed relating outcome of childhood ITP (i.e., intracranial hemorrhage) to platelet count. Dr. Sutor and Dr. Bussell were assigned to establish a European/North American registry of cases of intracranial hemorrhage in children with both acute and chronic ITP.

3. Evaluation of Children with Thrombosis

Laboratory (U. Nowak-Gottl, Germany) and clinical evaluation (M. Manco-Johnson, USA) of the neonate and child with thrombosis were discussed. Dr. Nowak-Gottl proposed a three-tiered algorithm for the laboratory evaluation of children with thrombosis. The primary evaluation should include testing for elevated lipoprotein (a), hyperhomocysteinuria, deficiencies of AT-III, protein C, and Protein S and evidence for the lupus anticoagulant (APTT and ACA). Individuals with a history of thrombosis, negative first-tier studies and a positive family history for early-onset thrombosis are evaluated further for dysfibrinogenemia, hypo/dysplasminogenemia, heparin cofactor II, HRGP, hyperlipidemia, and deficiencies of factor XII or factor V. Children with symptomatic thrombosis found abnormal only for factor V Leiden are further assessed for defects in fibrinolysis including TPA antigen and activity, PAI-1 activity and release with stasis. Evaluations include an initial evaluation at the time of thrombosis, follow-up at 3

to 6 months or after discontinuation of oral anticoagulation, and confirmatory family studies. Assay methodology was discussed. Dr. Manco-Johnson discussed necessary clinical methodology and documentation including determinations of thrombosis diagnosis, site, extent, underlying medical conditions and risk factors, treatment and outcome. The subcommittee suggested starting with diagnostic and outcome criteria. The two sets of recommendations will be developed for publication as recommendations of the SSC based upon prevailing best practice.

4. Lupus Anticoagulants in Children

Dr. Christof Male, Austria, presented long-term outcome data of 95 Austrian children with the lupus anticoagulant evaluated between 1969 and 1996. The data suggest that children manifest a higher rate of bleeding associated with low activities of prothrombin as compared with adults. Clinically significant abnormalities were determined in children who presented with bleeding or thrombosis, not in routine screening. Dr. Male suggested a multi-center collaboration to increase the data base and the subcommittee supported this recommendation.

5. Registries

Dr. Maureen Andrew, Canada, reported results of the Canadian and international registries for neonatal and pediatric thromboses since 1990. The benefits and limitations of registries were discussed. Registries have been useful to generate baseline data needed to plan prospective randomized clinical trials.

6. Catheter-related Thrombosis

Dr. Eric Grabowski, USA, discussed various issues contributing to thrombotic risk of catheters including placement, duration, size match to vessel, wall thickness, biomaterial, perfusate, and local flow dynamics. Dr. Grabowski recommended that initial attempts to study catheter-related thromboses should focus on placement and duration. Basic research efforts continue to be focused on the other issues.

7. Pregnancy-related Thrombosis in Women with Genetic Thrombophilia

Drs. Conard (France) and Walker (Scotland) discussed a clinical approach to evaluation, therapy and thrombosis prevention in women with genetic thrombophilia. They requested another year to work with Dr. Helgren in definition of issues before developing a formal subcommittee report.

**1998 MINUTES
PERINATAL/PEDIATRIC HEMOSTASIS**

Sunday, 21 June, 1998, 13:00-17:00

Cankerjev Dom

Ljubljana, Slovenia

Chair: M. Manco-Johnson, USA

**Co-Chairs: M. Andrew, Canada; M. Hellgren, Sweden; R. von Kries, Germany; A. Sutor,
Germany**

Approximately 20 persons attended the subcommittee meeting. All participated actively in the discussions.

The first half of the meeting was devoted to hypercoagulability and thrombosis in the obstetrical patient. Drs. Margreta Hellgren and Jacquie Conard presented a comprehensive summary addressing epidemiology, diagnosis, therapy and prophylaxis of thrombosis during pregnancy and the puerperium. The management of women with thrombophilia received special attention. An enormous effort was evident in the breadth and depth of the data and was appreciated by all present. A proposal was made to develop this report into Guidelines to be presented to this committee at the Washington meeting with publication recommendations at that time.

Dr. James Bussel gave an update on Neonatal Alloimmune Thrombocytopenia. It was proposed that an updated Guidelines paper on this topic (last done in 1991) should be prepared and presented at the Washington meeting in anticipation of publication. We would like to see these guidelines published as a joint recommendation of the Platelet Immunology and Perinatal/Pediatric Subcommittees.

Drs. James Bussel and Anton Sutor reported on their assigned task to determine the scope and correlates of intracranial hemorrhage in children with ITP. A questionnaire has been prepared, IRB consent has been drafted and the joint project should commence in North America and Europe by September. Preliminary results will be reported in Washington.

Dr. Sutor reported on the Subcommittee's position paper on Neonatal Vitamin K deficiency. This paper is recommended for publication. Dr. Sutor will add the requested statement on breastfeeding while taking oral anticoagulants and will share this recommendation with Dr. Hellgren to ensure that the obstetrical recommendations are identical.

Dr. Patti Massacotte reported on use and monitoring of 2 LMW heparin preparations in infants and children, Enoxaparin and Reviparin. It was proposed that recommendations for use of unfractionated heparin, LMW heparin and thrombolytic agents would be combined and prepared for publication from this Subcommittee. That manuscript should be completed this year.

The discussion on coagulation testing in children with thrombosis had to be abridged due to the absence of Dr. Nowak-Göttl and the dearth of time. These recommendations will be drafted as a Guidelines paper and circulated to committee members for comment. A final report will be presented in Washington.

New Business: After discussing a number of potential topics, the participants in the meeting expressed interest in future exploration of the following issues:

Obstetrical: evaluation and management of bleeding disorders in pregnant women.

Neonatal: DIC (to be done in collaboration with the DIC subcommittee with Dr. Keith Hoots as a liaison).

Pediatric: venous occlusive disease in transplantation and chemotherapy: epidemiology, pathophysiology and implications for therapeutic trials.

1999 MINUTES

PERINATAL/PEDIATRIC HEMOSTASIS

Sunday, 15 August 1999

8:00 to 12:00 PM

Room 30/31

Washington Convention Center

Washington, DC

Chair: M.J. Manco-Johnson, USA

Co-Chairs: M. Hellgren, Sweden; M.P. Massicotte, Canada;

A. Sutor, Germany

The Perinatal/Pediatric Subcommittee meeting was attended by approximately 200 persons. Participation was active, discussion was lively and substantial interest was expressed in the presented topics and activities.

I. Standardization of laboratory testing for coagulation abnormalities in children who present with thrombosis.

In the first part of the program, the types and prevalence of coagulation abnormalities detected in children presenting with thrombosis in various settings were reviewed and recommendations made, as follows.

Catheters, Dr. Tom Abshire, USA: Because of recent reports supporting the presence of genetic and acquired prothrombotic traits in the majority of children at the time of presentation with thrombosis, this group of infants and children would warrant a complete study.

Cancer, Leukemia, Dr. Ulrike Nowak-Göttl, Germany: An excess risk of thrombosis has been reported in the treatment of several pediatric malignancies. All episodes of thrombosis occurred in children with indwelling central venous catheters. The cost/effectiveness of screening children at the outset of therapy, and the need for prospective intervention trials in children identified with thrombophilia and cancer were stressed. In addition, the additive effect of chemotherapy was discussed. The association of an increased risk of venous thromboembolic events with the specific L-asparaginase obtained from Kyowa, Japan explained discrepant results of studies examining the relationship of thrombosis to L-asparaginase.

Stroke, Drs. Vinod Balasa, Ralph Gruppo, USA: The conclusion of Drs. Balasa and Gruppo was that a complete laboratory evaluation should be performed in children with stroke.

Hormones, Dr. Marjolein Peters, The Netherlands: Dr. Peters recommended that girls treated with high dose estrogens be evaluated, especially for free protein S level, prior to commencing therapy.

Bone Marrow Transplantation (BMT)/Venous Occlusive Disease (VOD): Dr. Donna DiMichele, USA: National collaborative groups should be utilized to collect data needed to develop recommendations regarding coagulation screening in children undergoing BMT and/or diagnosed with VOD.

Neonatal, Dr. Wolfgang Muntean, Austria: The consensus of the subcommittee participants was that the in the premature infant thrombosis is almost always related to blood flow, vascular obstruction by catheters and consumptive coagulopathies whereas the well term infant with thrombosis is more likely to manifest a genetic thrombophilia. Routine coagulation testing was recommended for term infants with thrombosis.

Antiphospholipid antibodies, Manco-Johnson, USA: Although more data is needed, children presenting with venous thromboembolism should be evaluated for the lupus anticoagulant and children with stroke should be studied for anticardiolipin antibodies. In children with thrombosis associated with SLE or varicella, the prevalence of antiphospholipid antibodies is quite high (70-80%). The overall prevalence of APA in neonates with stroke is probably low.

The Subcommittee resolved to draft a position paper making recommendations regarding laboratory coagulation testing of children with thrombosis in the absence of adequate data, and proposing future studies to obtain information necessary for a definitive recommendation. This will be accomplished in the next nine months and submitted prior to next year's meeting.

II. Monitoring of long-term anticoagulation was reviewed by Drs. Patti Massacote (Canada) and Paul Monagle (Australia).

III. Intracranial hemorrhage in ITP, Dr. James Bussel, USA:

Dr. Bussel and Dr. Sutor reviewed consensus papers from North America, Germany and the UK. A decision was made to develop a consensus paper from this committee specifically regarding current areas of consensus and lack of consensus around "need to treat, " not addressing the treatment *per se*, for infants and children with ITP relative to platelet count. This paper will also be submitted prior to next year's meeting. The second activity proposed in this section is continuation of an international registry of cases of intracranial hemorrhage in children with ITP. Because all treatment is designed to prevent this dreaded complication, factors associated with ICH determined by the registry will be useful to design prospective studies, intervention trials and future recommendations around treatment of ITP in children.

IV. Papers: Dr. J. Conard presented on behalf of Dr. Hellgren who was unable to attend. A summary of the recommendations for diagnosis and treatment of thromboembolism during pregnancy and the puerperium were presented. Input was received from participating committee members. The paper has undergone numerous drafts and will be submitted to the SSC Publications Review Committee within two to three months.

V. New Business:

Rheology, Eric Grabowski, USA: Dr. Grabowski presented an elegant paper demonstrating that neonatal endothelial cells support increased activation of Factor Xa and an increased ability to express tissue factor in response to increased shear stress *in vitro*. In his model the neonatal phenotype is controlled by shear stress. Transcription of tissue factor as well as levels of TFPI and TPA was comparable in the neonatal and adult models. There was consensus that this type of model is needed to address many remaining unknowns in neonatal hemostasis and the subcommittee should expand its interest in the neonatal endothelial cell. Future meetings will devote more time to neonatal rheology and the subcommittee requests that members involved in this area of research submit suggestions for next year's program.

PERINATAL/PEDIATRIC HEMOSTASIS

16 June 2000

08:00 to 12:00

Room 0.8

Maastricht Meeting and Convention Center

Chairman: M.J. Manco-Johnson--USA

**Co-chairmen: E.F. Grabowski--USA; M. Hellgren--Sweden; M.P. Massicotte--Canada;
U. Nowak-Gottl--Germany; M. Peters--The Netherlands; A. Sutor--Germany**

The chair, all co-chairs and approximately 40 Subcommittee members were present. Issues discussed were as follows:

1. Recommendations for laboratory evaluation of children with thrombosis: This project has been written as an official recommendation of the Subcommittee. M. Manco-Johnson presented the paper to the Subcommittee and each major point was voted upon. Minor additions or changes were agreed upon. The finished product will be sent to Dr. Francis.
2. LMWH dosing in infants and children: Data from four very small pharmacokinetic studies were presented and evidence for increased dose and monitoring requirements in children were discussed. The Subcommittee members agreed that there is sufficient evidence to warrant formal study. A working group was constituted including M. Manco-Johnson (Colorado, USA), E. Grabowski (Massachusetts, USA), U. Nöwak-Gottl (Germany), U. Peters (The Netherlands), R. Liesner (London, UK), J. Tusell (Barcelona, Spain) and M. Williams (Birmingham, UK). The working committee will develop a data collection instrument to be used in an international collaborative study of LMWH dosing based upon plasma anti-Xa level measured at 3 to 4 hours after a subQ dose (4 hours is preferred as this represents the dominant clinical practice). A report will be due at next year's meeting.
3. Arterial versus venous thrombosis in children. A stimulating presentation was give by E Grabowski in which evidence was presented to substantiate low flow currents around arterial catheters, damaged endothelium and arterial prostheses. These localized low-flow currents would promote "venous-like" red cell clots in children. This data supports application of the recommendations developed for thrombophilia evaluations (as discussed in #2, above) to children with arterial thrombosis.

4. Lp(a) levels in children were discussed by U Nöwak-Gottl. Lp(a) was shown to contribute a six-fold increased risk for thrombosis. Familial thrombotic disease has been related to higher levels of Lp(a) (> 30 mg/dl) and isoforms consisting of fewer kringle 4 repeats (14 to 22 versus greater than 28). Neonates were found to have lower levels of Lp(a) and a skewing toward the isoforms comprised of more kringle repeats. By twelve months of age, results in children are similar to that of their parents. African children have higher levels of Lp(a) but this does not appear to confer an increased thrombotic risk in that population. The IFCC conducted an evaluation of 39 assay systems and found substantial problems with half of the assays. The inadequate assays did not show a linear dose-response of Lp(a) and dilution curves of unknowns were not parallel to the standard curve. The ELISA assays performed better than immuno-nephelometric or immuno-turbidometric assays. Recommendations for assays included use of a universal standard and two-antibody ELISA assays. Thawed and refrozen samples should not be used for assay and prolonged storage affected assay results. Consensus was reached that large sample sizes are needed to develop ethnic specific-normal values and to investigate the relationship of Lp(a) to neonatal and pediatric venous and arterial thrombosis. Dr. Nöwak-Gottl will develop a proposal to compare results generated in different laboratories, develop appropriate control groups and correlate levels measured in children with venous and arterial thrombosis.

5. Diagnosis and management of thrombosis during pregnancy: the Anticoagulant and Perinatal Subcommittees jointly developed this project. Drs. J Connard and M Hellgren read the report. Each major point was discussed and voted upon by the members present. The document will be edited to include suggestions made, circulated to a list of members who registered willingness to review the document and will be sent by M Manco-Johnson to Dr. Francis within two months.

6. A possible inclusion of women's coagulation problems into the Perinatal/Pediatric Subcommittee was discussed. It was decided that the scope of work by such an expanded subcommittee would be too broad and would dilute the efforts of both groups. A formal recommendation will be sent to Dr. Francis suggesting that a new subcommittee be established for coagulation problems in women and that coagulation disorders during pregnancy be transferred to such a subcommittee. It was recommended that collaborative activities be conducted between the Perinatal/Pediatric Subcommittee and a new subcommittee for Coagulation in Women.

7. ITP in children: J Bussell (New York, USA) presented the major points of an SSC paper that has been written comparing recommendations and/or consensus developed independently by the UK and the ASH (US). A Sutor presented German recommendations on childhood acute ITP. S Davidson (London, UK) and C Van Geet

(Leuven, Belgium) volunteered to review the final draft of the manuscript and suggest any changes needed.

8. Severe protein C deficiency: B Moritz (Vienna, Austria) reviewed the development and compassionate use of a human plasma-derived protein C concentrate. Plans to complete formal pharmacokinetic studies and begin phase II/III treatment trials were outlined. The Subcommittee approved these plans.

PERINATAL/PEDIATRIC HEMOSTASIS

7 July 2001
08:00 to 13:00
Room 251
Palais des Congrès

Chairman: U. Nowak-Gottl--Germany
Co-chairmen: E.F. Grabowski--USA; M. Hellgren--Sweden; A.S. Kemahli--Turkey;
M.J. Manco-Johnson--USA; M.P. Massicotte--Canada; W. Muntean--Austria;
M. Peters--The Netherlands

The chair and co-chairs and more than 200 participants/ subcommittee members were present. Issues discussed were as follows:

1. *Epidemiology, diagnosis, management and prophylaxis of venous thrombosis during pregnancy*: This topic was presented by M. Hellgren. She stated that hereditary or acquired thrombophilia increases the risk of VTE and that screening for thrombophilia should be performed following obstetric complications such as early-onset severe preeclampsia, abruptio placentae, severe IUGR, repeated fetal loss and IUFD. In addition, M. Hellgren pointed out that objective diagnosis verification by suitable imaging methods is mandatory. Treatment modalities of VTE during pregnancy, e.g. i.v. infusion of unfractionated heparin (UFH) followed by s.c. UFH or low molecular mass heparin (LMMH) until delivery were discussed as well as the use of prolonged anticoagulant treatment with oral anticoagulants or s.c. LMMH post partum. Thromboprophylaxis with s.c. LMMH is suggested during pregnancy for women with previous VTE and thrombophilia, recurrent VTE, hereditary antithrombin deficiency without previous VTE, and antiphospholipid antibody syndrome. In addition to M. Hellgren, B. Brenner presented data indicating that inherited thrombophilia is associated not only with gestational thromboembolism but also with fetal loss, intrauterine growth retardation, preeclampsia and placental abruption. The antithrombotic therapy in this setting was further discussed. In addition, the placenta as the target organ for future research was pointed out.
2. *Prothrombotic risk factors and imaging methods in ischemic stroke in children*: F. Kirkham (London) and R. Sträter (Münster) reported on ischaemic stroke in children. Both underlined the importance of prothrombotic risk factors at the onset of the disease and the possible role in recurrent stroke. In addition, they pointed out that stroke types may influence recurrent stroke and that an adequate imaging work-up is mandatory in classifying stroke children. The future of therapeutic multicentre studies was discussed.
3. *Deep venous thrombosis in children*: Dr. Mitchell reported the results from the PARKAA Trial (Prophylactic antithrombin replacement therapy in kids with acute lymphoblastic leukemia treated with asparaginase) in which imaging methods, i.e. venography and ultrasound, were compared. She concluded from the data obtained that venography was superior to ultrasound in detecting thrombosis in the central venous system, whereas ultrasound was more sensitive in detecting venous thrombosis in the jugular veins. M. Briones&T. Abshire discussed a management report on catheter-related thromboses in

children older than 12 months of age. M. Peters presented an objective new but not yet validated scoring system in adolescent patients with deep venous thrombosis for the use of heparin prophylaxis. This scoring system should be validated in different ethnic groups before it can be used routinely. M. Manco-Johnson reviewed data on TPA thrombolysis in children and concluded that the value of TPA thrombolysis compared to standard anticoagulant therapy in reducing morbidity should be studied in prospective clinical trials. P. Massicotte reported on bone mineral density in a pediatric cohort patients suffering from DVT receiving long-term warfarin therapy. This paper gave evidence that BMD remains significantly decreased, with bone formation more affected than bone resorption, resulting in a net result of increased bone resorption. The need for further studies in the field were discussed. M. Peters reported on postthrombotic syndrome in children after venous thrombosis. Data from their study suggested that approximately two-thirds of children with DVT of the limbs are at risk of developing postthrombotic syndrome, with a higher risk in children carrying prothrombotic defects, suffering from recurrent thrombosis, and with a first onset during adolescence. The need to study compression stockings in these children was discussed.

4. *Normal values of hemostatic parameters in the pediatric population:* H.G. Koch reported on fasting homocysteine concentrations in healthy children and pediatric patients with thromboembolism. He reported that children carrying Hcy concentrations > the 90th age-dependent percentile have an increased risk of developing thromboembolism. In addition, in the upper Hcy quartile the odds ratio for suffering thrombosis was significantly increased also in neonates, infants and children. V. Balasa reported on prothrombin and PAI-1 in healthy children. He stated that a significant relationship between the G2021A allele and elevated plasma prothrombin levels was not recorded among children. The PAI-1 4G/4G polymorphism was associated with elevated PAI-1 activity levels in children. The PAI-1 genotype was an independent, significant determinant of PAI-1 antigen levels in children as well. The 4G allele of the PAI-1 gene is more commonly present among Caucasians than among African-Americans variants and its role in pediatric thromboembolism has to be evaluated in future studies. S. Israels reported on the evaluation of platelet function in children using the PFA-100 platelet function analyzer. Mean closure times (CTs) are significantly shorter in neonates, and slightly, but not significantly, longer in healthy children than in adults, and similar normal ranges can be used for screening children with bleeding disorders. CTs can be used for simple and accurate evaluation of the response to desmopressin in children with vWD and platelet function abnormalities. Patients with type 1 vWD consistently showed correction of CTs, while type 2 patients showed variable results that correlated with changes in ristocetin cofactor activity (RCoF). Some patients with partial storage pool deficiency or secretion defects also showed CT correction following desmopressin. For patients with vWD not responsive to desmopressin, vWF factor concentrates did not correct the CT, although levels of vWAntigen and RCoF were increased. In comparison to older children and adults, mean CTs of cord blood from healthy neonates are significantly shorter. E.F. Grabowski reported on platelet adhesion/aggregation in flowing blood in pediatric hemostatic disorders. He concluded that platelet function under physiologic flow conditions is clearly more informative regarding hemostasis (or thrombosis) than platelet count or aggregation in platelet-rich plasma, and may very well correlate more significantly with clinical bleeding (or thrombosis). Nicole Schlegel introduced the

results of a study on integrin expression and function in neonatal platelets. She reported that a significant defect in GPIIb/IIIa expression and function and a specific GPIb behavior were registered in neonatal platelets. B. Kehrel introduced also normal age-dependent values for the distribution of platelet membrane glycoproteins in neonates, children and young adults. She demonstrated first results showing that, despite neonatal platelets expressing normal amounts of glycoprotein (GP) Ia/IIa, GPVI and GPIb/V/IX, neither CD62-P expression nor CD63 expression nor fibrinogen binding was induced by collagen (up to 1.5 µg/ml), whereas 0.5 µg/ml induced maximal activation of adult (age 20-35 years, n=25) platelets. In contrast ristocetin-induced vWF-binding to neonatal platelets was increased significantly. Even 0.3 to 0.5 mg/ml ristocetin induced maximal vWF-binding. 0.8 to 1.0 mg/ml ristocetin is needed to induce maximal vWF-binding in normal adult platelets. She concluded that knowledge of normal platelet functions in children are essential for the reliable diagnosis of platelet function disorders.

5. *Influence of factor VIIa on thrombin generation:* A. Chan reported the on influence of exogenous factor VIIa on thrombin generation in cord plasma of full-term and preterm infants. He found that FVIIa enhanced IIa generation in plasma from different age groups, with the effect being more pronounced in plasma from preterm newborns, possibly due to increased levels of plasma TF.
6. *Hemophilia:* M. Manco-Johnson and P. Petrini introduced the development of international standards for assessment of physical outcomes in children with hemophilia. The WFH and three new scales were compared in 43 hemophilic children. The three new scales all showed better correlation with the WFH pain instrument than the original WFH physical examination instrument ($p < 0.01$ for each of the new instruments vs. > 0.05 for the WFH instrument). In addition, results of the new Colorado child physical examination instrument best conformed with a normal distribution ($p=0.35$) and displayed better overall statistical performance. This instrument should be studied further in prospective, longitudinal clinical trials of young children.
7. *Thrombocytopenia:* J.. Bussel reported on a series of intracranial hemorrhages in ITP. In addition, he introduced a newly developed registry of non-immune thrombocytopenia. The Non-Immune Thrombocytopenia registry will begin in the United States, Canada, and Europe. The intention is to identify cases of chronic thrombocytopenia that are not ITP, including amegakaryocytic thrombocytopenia (CAMT).

Perinatal/Pediatric Haemostasis

July 19, 2002

14:00 to 18:00

Plaza Room

Boston Park Plaza Hotel

Chairman: U. Nowak-Göttl, Germany

Co-chairs: E. F. Grabowski, USA; M. Hellgren, Sweden; A. S. Kemahli, Turkey;

G. Kenet, Israel; P. Massicotte, Canada; W. Muntean, Austria;

M. Peters, Netherlands

The chair and co-chairs and approximately 55 Subcommittee members were present. Issues discussed were as follows:

1. Platelets and Thrombin generation:

Thrombocytopenia: J. Bussel summarized again the available data on intracranial hemorrhage (ICH) occurring in acquired childhood ITP in the US and other countries. Causative factors, predictors and outcome were discussed as a basis for an understanding of the disease. No controlled data are available to date on whether treatment can prevent ICH from occurring during childhood ITP. Thus, multicenter controlled therapeutic trials are recommended (study end-point: ICH).

V. Bardet et al. reported on inherited thrombocytopenias with respect to new diagnostic techniques (flow cytometry, genetic analysis, ultrastructural studies) and therapeutic approaches. A consensus was discussed.

Thrombin generation in neonatal plasma: W. Muntean et al. reported on the thrombin generation capacity in neonatal plasma compared with adult plasma. The authors focused on the role of antithrombin and tissue factor pathway inhibitor (TFPI). They clearly demonstrated that, under physiological conditions (low plasma dilution and low amounts of TF), cord plasma clots earlier than adult plasma, and FXa- and FIIa-generation starts earlier, due mainly to low levels of TFPI and AT. The authors concluded that, despite low levels of procoagulatory factors, sufficient hemostasis is achieved in neonatal plasma.

2. Venous thrombosis in children:

Testing of prothrombotic risk factors and pediatric controlled studies: Based on the presentations given (P. Mathwey, M. Peters & F. Rosendaal, E. Grabowski & M. Manco-Johnson) and the literature available, important questions concerning pediatric population-based studies were discussed. One of the main questions was whether every child with symptomatic venous thrombosis should be tested for prothrombotic risk factors or whether a distinction should be made between low/intermediate- and high-risk patients. It was furthermore discussed whether meta-analysis of literature data on the incidence of genetic risk factors will help to classify children at risk, and whether meta-analyses have (dis)advantages compared with controlled multicenter studies in children and vice versa. Another question was whether pediatric studies should always be controlled by using age-matched healthy children. The last issue raised at this

session was whether the testing of asymptomatic family members is indicated, and if so in what cases.

3. Coagulation factor concentrates:

Protein C-deficiency: C. Escuriola et al. reported on indications, dosages, and laboratory monitoring during the use of human protein C concentrate in children with congenital and acquired protein C deficiency. Data obtained from case series suggest that human protein C is effective in treating congenital protein C deficiency. Six out of eight children with acquired protein C deficiency and with severe disturbance of the microcirculation due to meningococcal septicemia survived after the administration of human protein C concentrate. The authors conclude that controlled studies should be carried out in children to obtain evidence-based data on the cost/benefit ratio of human protein C concentrate. Furthermore, comparative studies between human protein C concentrate and activated protein C concentrate are recommended with respect to clinical benefits as well as to potential side effects.

Recombinant factor VIIa (rFVIIa): E. Grabowski discussed the in vitro hypothesis of inactivated r-FVIIa being used in preclinical studies to interrupt the TF pathway of coagulation. This hypothesis is based on experimental data showing the expression of enzymatically active TF-Factor VIIa complex by HGECs exposed to various combinations of TNF-alpha and Shiga toxin-1.

Von Willebrand disease: B. Zieger reported on indications, dosages, and duration of application of von Willebrand factor concentrate or Desmopressin in children with different types of von Willebrand disease. Unclarified issues, e.g., for what ages Desmopressin is acceptable, adequate postoperative management in view of the possibility of volume overload and hyponatremia, and the possible intranasal application of Desmopressin should be clarified in controlled prospective studies in children.

4. Pediatric Stroke

Population-based data on ischemic stroke in pediatric patients were summarized by leading stroke experts from ten countries (M. Bonduel, Argentina; W. Muntean et al. Austria; G. deVeber et al., Canada; I. Husson et al., France; R. Straeter et al., Germany; G. Kenet et al., Israel; S. de Vries et al., The Netherlands; A. Kemahli, Turkey; V. Ganesan & F. Kirkham, United Kingdom; J.K. Lynch et al., US). Underlying diseases, imaging methods, presence of prothrombotic risk factors, and therapeutic options were discussed. A consensus paper on uniform stroke classifications, imaging methods, and laboratory screening as a basis for international multicenter therapeutic trials was proposed.

Perinatal/Pediatric Haemostasis

July 13, 2003

08:00 to 12:00

Hall 11

The International Convention Center, Birmingham

Chairman: U. Nowak-Göttl, Germany

Co-chairs: B. Brenner, Israel; E. F. Grabowski, USA; G. Kenet, Israel; P. Massicotte, Canada;
P. Mathew, USA; W. Muntean, Austria; N. Schlegel, France

The chair and co-chairs and approximately 240 Subcommittee members were present. Issues discussed were as follows:

1. *Perinatal hemostasis*: This issue was presented by B. Brenner, G. Kenet, and G. Cvirn. B. Brenner reported on the favorable outcome of newborns of mothers treated with LMWH due to previously reported pregnancy complications, and G. Kenet et al. underlined the need for further research with respect to the role of thrombophilia in perinatal complications in preterm and term babies. With respect to a clinically observed well-functioning hemostasis in neonates G. Cvirn et al. demonstrated that, despite different amounts of plasma clotting factor inhibitors in term infants compared with adults, the rate of thrombin formation is similar.
2. *Thrombosis issues*: These topics were presented by C. Male, G. deVeber, F. Kirkham, G. Kenet and R. Sträter. C. Male et al. demonstrated the need for standardized research with respect to central line-associated (CVL) thrombosis in children. The authors pointed out that CVL location and CVL insertion technique are responsible in the majority of cases for the different rates of thrombosis diagnosed with objective imaging methods. G. deVeber, F. Kirkham, G. Kenet and R. Sträter reported on cerebral venous thrombosis (CVT) in children with respect to clinical presentation, diagnostic imaging methods, underlying diseases, treatment and outcome. All authors agreed that CVT in children is a multifactorial disorder and underlined the need for larger multi-national studies or registries to receive additional and comparable data of outcome and treatment safety. The future of therapeutic studies was discussed.
3. *Anticoagulation issues/new study protocols*: This topic was covered by P. Massicotte, L. Mitchell, A. Chan, and B. Zieger. P. Massicotte and L. Mitchell pointed out that randomized clinical trials are urgently required in children to determine the safest and most effective heparin therapy, UFH as well as LMWH, for venous thrombosis. B. Zieger underlined the need for further studies in children with heparin-induced thrombocytopenia type II treated with recombinant hirudin. In an animal model A. Chan introduced a new anticoagulant (antithrombin-heparin covalent complex to be coated to CVLs) which shows a clear reduction in thrombus formation in comparison with uncoated CVLs.

4. *Bleeding disorders:* P. Mathew reported on the use of recombinant factor VIIa (rFVIIa) in the treatment of non-hemophilic bleeding disorders in children. He summarized the data previously published on 30 children. However, since no controlled studies are available, P. Mathew and the SSC members concluded that randomized trials are urgently needed to prove the efficacy and safety of rFVIIa in bleeding situations of non-hemophilic children. J. Bussel discussed the need for a national and international registry to record more information on clinical presentation, treatment and outcome of acute and chronic ITP in children.
5. *Discussion:* A position paper on "platelet function disorders/acute and chronic ITP" introduced by N. Schlegel as a possible SSC report was discussed. B. Brenner presented an SSC position paper on "Thrombophilia and pregnancy complications in cooperation with the working group on Women's Health Issues: Maternal, fetal and newborn issues", and L. Mitchell introduced the position paper on "Recommendations for the use of both ultrasound and venography for diagnosis of venous thromboembolism in children". The SSC chair and co-chairs agreed to the three SSC report proposals.

Perinatal/Pediatric Haemostasis

June 18, 2004

14:15 to 18:15

Piccolo Teatro Room
Fondazione Giorgio Cini

Chairman: P. Massicotte, Canada

Co-chairs: B. Brenner, Israel; G. Kenet, Israel; P. Mathew, USA; P. Monagle, Australia;
W. Muntean, Austria; U. Nowak-Göttl, Germany; N. Schlegel, France

Congenital Heart Disease

1. *Cardiopulmonary Bypass (CPB) and Thrombosis: Stroke* – G deVeber / A. Chan / P. Massicotte

There are minimal amount of literature in the topic of stroke in children post-CPB. There is only one abstract that estimates the incidence to be 0.4%. Approximately 50% of these children suffered from significant neurological morbidity. Other studies estimated the incidence of neurologic abnormalities (including stroke) to be 25% in children undergoing cardiac surgery. The studies are limited by methodologic issues ie. small, retrospective and not valid testing (neurocognitive in neonates). There have been studies in children to prevent neurologic injury secondary to CPB. Most studies suffer methodologic flaws.

Recommendations: The subcommittee recommends a literature review to be submitted by October 2004 with the recommendations that more studies are urgently needed.

2. *Thromboprophylaxis of mechanical heart valves* – M. Bauman / P. Massicotte/ A. Chan

Children receiving warfarin as primary prophylaxis for mechanical heart valves who require interventional procedures (cardiac catheterization) must have reversal of warfarin pre-procedure. Many centres hospitalize children the night before the procedure to administer intravenous heparin. The use of unfractionated heparin subcutaneously the night before the procedure was described. The children received age appropriate UFH dosing (weight kg X u/kg/hrX number of hours of anticoagulation coverage required) and a APTT the morning before the procedure was normal in 99% of children. There were no adverse events in this cohort (bleeding or thrombosis) This appears to be a safe option for anticoagulation reversal in this population and allows children to remain home until the time of the procedure. Comments from international colleagues described other reversal methods such as the use of low molecular weight heparin (LMWH) the night before the procedure.

Recommendations: The committee suggested that further lab studies including anti- factor Xa and anti- factor IIa levels were needed to provide more data re UFH clearance.

3. *Oral anticoagulant therapy in infants younger than 12 months of age.* - **M. Bonduel**

Warfarin, acenocoumarol and phenprocoumon are the VitK antagonists used pediatric patients with thrombotic complications in different countries according to their experience and familiarity with these drugs. The studies of warfarin and acenocoumarol highlight the difficulty of their use in infants < 12 months of age. This age group required increased doses to achieve and maintain target INRs, as well as more frequent testing, and adjustments of loading dose to achieve the target INR faster with no overshooting.

Increased alpha 2 macroglobulin levels and decreased thrombin generation were described in the pediatric population compared to adults receiving warfarin. Therefore the intensity of the oral anticoagulant therapy may vary in children respect to adult patients

Recommendations: The committee suggested that further studies of warfarin, acenocoumarol and phenprocoumon requirements are needed. The factors that could interfere in the action of OA agents in this age-group should be identified (i.e, Vit K use, diet, drugs, cytochrome p450 reductase levels and genotype).

Risk factors for Venous Thrombosis/Thromboprophylaxis

1. *Central Venous Lines: Thromboprophylaxis* – **L. Mitchell/S. Revel Vilk**

Central venous lines appear to be a strong risk factor for the development of thrombosis in children. The incidence has been estimated at least 20% through prospective cohort studies and is dependent on the method of diagnosis. The outcomes include death and morbidity of post thrombotic syndrome and recurrence. A proposal for the subcommittee to recommend a study to investigate the safety and efficacy of thromboprophylaxis was suggested.

Recommendations: International colleagues felt that there was not enough data re outcomes and that certain populations of children may have varying risk with the development of thrombosis related to CVLs. Therefore, the subcommittee was reluctant to state that a thromboprophylaxis study is recommended. However, it was agreed that a communication from the subcommittee should include that risk assessment of different disease cohorts of children should be carried out. This would be followed by recommendations for a study in those cohorts at highest risk of developing VTE with adverse outcomes.

2. *Factor VIII levels and lipoprotein (a) Standardisation normal values and risk cutoffs for thrombosis in children* **U. Nowak Gottl/ E. Grabowski**

Lipoprotein (a) and persistently elevated FVIII levels have been shown to be a risk factor for venous thromboembolism in children. However, the assays for lipoprotein (a) and FVIII require standardization in order to make studies comparable.

Recommendations: The subcommittee agreed that discussion should be carried out re a study with central laboratory testing . There was agreement that more studies to determine the relationship of FVIII to the development of VTE in children are necessary.

Treatment of Thrombosis

1. *Treatment of venous thrombosis - E. Chalmers/ H. Van Ommen*

The studies on the treatment of VTE in children using LMWH were reviewed . There is only one randomized clinical trial (RCT) estimating the safety and efficacy of LMWH for treatment of VTE in children. Discussion revealed differing treatment practices internationally.

Recommendations: The subcommittee agreed to set up an expert group to design a survey to determine the treatment practices. This will be a properly designed survey that will be completed and presented in Australia 2005.

2. *Effects of hirudin and heparin in neonatal plasma - Baier/ W. Muntean*

There have been in vitro studies carried out using cord plasma spiked with heparin and hirudin. Results suggest that neonates respond differently than adults to thrombotic stimuli and the response depends on the strength of the stimulus. Neonates may require different concentrations of anticoagulants than adults to achieve the same effect.

Antiphospholipid Antibodies

Risk of thrombosis in children with APLA – C. Male

There is good evidence of a high risk of thrombosis in children with SLE and APLA.. The association of APLA with TE found in pediatric cohorts are stronger than those found in adult studies. Few children with SLE who are negative for APLA develop TE. Lupus anticoagulant is a stronger predictor of the risk of TE than anticardiolipin antibodies, anti beta 2 glycoprotein antibodies and anti prothrombin antibodies.

In children without underlying SLE case reports describe associations of APLA and severe thrombotic complications (primary APLA syndrome). Currently, it is unknown what the risk of TE is in well children with APLA. Increased prevalence of APLA are found in children who suffered from stroke compared to controls .However, recent evidence suggests, in general, APLA presence is not associated with an increased risk of recurrent stroke.

Recommendations: The subcommittee recommends that the data on stroke and APLA in children be published in a Position paper with the recommendations that more studies are urgently needed in this area especially in primary prophylaxis of patients with APLA and SLE.

Monitoring of Anticoagulation

1. *Anti-factor Xa monitoring LMWH therapy in children* – **W. Muntean**

No definite conclusions about the benefit of anti Xa monitoring and association of levels with bleeding can be made. Whether target levels recommended for adults are adequate for infants and children and whether anti factor Xa monitoring in pediatric patients can be made on the basis of the limited data..

Recommendations: There will be a subgroup within the committee to discuss how to assess risk of bleeding in children receiving LMWH. This group will be the same as the treatment subgroup.

Treatment of Bleeding

1. *FVIIa use in non hemophiliac children* - **P. Mathew/Bomgaars**

There is little data on the use of FVIIa in nonhemophiliac children other than case reports and small case series. A cohort study in children with liver disease and coagulopathy was proposed to determine the pharmacokinetics and estimate the safety and efficacy using surrogate markers .

Recommendations: A subgroup to make recommendations re studying the use of FVIIa in children will be set up. This may result in carrying out studies or an international registry.

Antiplatelet Therapy

1. *ASA resistance, Testing for resistance and Dosing* - **M. Rand/ M. Albisetti**

There is no standard definition for ASA resistance. In terms of a laboratory definition ASA resistance has been considered as the failure of ASA to produce an expected inhibitory response on one or more lab measures of thromboxane-dependent platelet activation/aggregation. The lab investigations include metabolites of thromboxane A2 or thromboxane A2 dependent responses. A small study in children with arterial ischemic stroke has found a 25% lab determined non-response to ASA therapy. Larger prospective studies are required to explore the ASA resistance and the predictive value of platelet activation parameters.

Recommendations: There will be discussions with Drs. Michelson and Rao (Chair and Co-chair of the Working Group on Aspirin Resistance of the Platelet Physiology Subcommittee) re the definition of ASA resistance.

Predictors of Bleeding

1. *Coagulation tests as predictors of Bleeding in CPB: New ways to predict bleeding /When should we test* – **G. Kenet/ N. Schlegel**

There are various new lab techniques available to monitor coagulation. However, it is unclear which of these techniques will be of clinical use in children.

Recommendations: It was agreed that the subcommittee should continue to focus on this area.

Perinatal/Pediatric Haemostasis

August 7, 2005

08:30 to 12:00

Sydney Convention Centre

Chairman: P. Massicotte, Canada

Co-chairs: G. Kenet, Israel; P. Mathew, USA; P. Monagle, Australia;
W. Muntean, Austria; U. Nowak-Göttl, Germany; N. Schlegel, France

Joint Session with the Scientific Subcommittee on Control of Anticoagulation

Chairs: S Schulman/ P Massicotte

New anticoagulants for pediatric use; lessons from adults

Jeff Weitz gave an overview of the development of new anticoagulants over the past few years, with emphasis on the lessons learnt and possible implications for the pediatric population. He described the development of heparins towards lower molecular weight with problems regarding decreased clearance in case of renal impairment, lack of specific antidotes and long half-life. New, selective anticoagulant agents have usually rapid onset and offset, a wide therapeutic window and no or reduced need for monitoring, but pediatric data is lacking as well as specific antidotes. A comment from the audience was that argatroban and bivalirudin, both approved drugs, are in clinical trials in the pediatric population.

Recommendation: It is important to ensure that some of the new anticoagulants will fit the needs of the pediatric population, for example with parenteral (subcutaneous) administration, no need for monitoring, not contraindicated in case of hepatic failure etc.

Towards a unified definition of major hemorrhage in clinical trials.

I. Non-surgical studies

Report S. Schulman

The process from discussion at the previous SSC in Venice 2004 was recapitulated briefly. The recommendation was published as a full length paper in JTH in April 2005. The European regulatory authority, EMEA, has been contacted and expressed interest in possibly adopting the recommendation but preferred to have the complete set, including recommendations for orthopedic and general surgery studies. Informal contacts have also been taken with FDA, and there is a growing interest there for possible issues of harmonization.

Plan: Encourage the process for similar recommendations in surgical studies and to further develop the contacts with EMEA and FDA.

II. Surgical studies – orthopedic.

Update. G. Raskob

The Working Party on Bleeding Complications in Orthopedic Studies has identified a large variety of definitions used in their field by performing a systematic literature review. Traditional measures of severity of bleeding have limitations in the early postoperative period. There is a definite need to include the surgeon's assessment of the surgical site bleeding.

Recommendations (preliminary): 1) There is a need for explicit reporting for the surgical site, which must be distinguished from other bleeding. 2) A blinded assessment should be done by a surgeon regarding the clinical importance of the bleeding at surgical site. 3) Bleeding index and clinically important bleeding should be reported independently as separate outcomes. 4) A clinically important bleeding at the surgical site if it leads to wound dehiscence, infection, re-operation, prolonged hospital stay or contributes to myocardial infarction, stroke or death, as assessed by an independent adjudication committee. The WP will accelerate their pace of development of the recommendations and will endeavor to get this published within the next 12 months.

III. Surgical studies – general.

Update. D. Bergqvist.

This issue is even more complicated than the orthopedic procedures, since the surgical procedures are less standardized in general surgery and the severity of the procedures vary greatly. Gynecologic procedures may differ a lot from other general surgery. The transfusion requirements are influenced by more or less conservative policies.

Recommendations (very preliminary): Major bleeding is tentatively defined as 1) leading to death, 2) leading to transfusions or endovascular hemostatic procedures, or 3) occurs in critical organs.

Plan: To form a working party within the next few months to continue the development of a unified definition.

The Use of Heparin in Children. **P. Monagle**

Unfractionated heparin (UFH) is the anticoagulation of choice in infants and children who are at high risk of bleeding (peri surgery, trauma, chemotherapy) because of ease of reversibility (protamine sulfate) and short half life. During cardiopulmonary bypass and extracorporeal membranous oxygenation, UFH is currently the anticoagulant agent of choice. However, infants and children do not respond to UFH in the same way as adults. The activated partial thromboplastin time (aPTT), a surrogate measure of UFH level, does not correlate to increasing levels of heparin in the same fashion as in adults. In fact, if comparing therapeutic anti factor Xa levels to corresponding aPTT levels, in infants and young children the therapeutic aPTT ranges are much higher than those in older children and teenagers. This difference may relate in part to developmental haemostasis differences, but there may be other different mechanisms of interaction compared to adults.

Recommendations: The difference response to unfractionated heparin between adults and children will be determined. A subgroup lead by Dr Monagle will determine how best to monitor UFH in neonates and children. This will be submitted as a position paper to the SSC.

***HIT in children* A. Greinacher**

The literature in adults with HIT was summarized. In neonates and children, heparin induced thrombocytopenia is rare (< 1%). Most infants who develop antibodies have underlying cardiac disease and develop antibodies post cardiac surgery. In adolescents who develop HIT, the most common indication for unfractionated heparin is the treatment of venous thromboembolism. The testing for HIT in children has not been standardized and cut off values for abnormal must be established.

Recommendations: A standardized approach to the diagnosis of HIT in children must be established. Dr Greinacher will lead a subgroup to develop a diagnostic approach in children which will be submitted as an SSC position paper.

Bleeding

Treatment of Bleeding

FVIIa use in non hemophiliac children: International Registry(ISTH Study) - P. Mathew/ J. Blatny

The use of FVIIa is increasing internationally in non haemophilic children despite the lack of properly designed studies. The establishment of an international web based registry to record and follow those children is important to provide an estimate of safety and efficacy in the absence of randomized controlled trials.

SevenBleep Registry is a web based International Registry which has just gone live. The Registry can be accessed from the ISTH home page.

Recommendations: Encourage international health professionals using FVIIa in non hemophiliac children to enter data in registry to estimate safety and efficacy of the product. Users must ensure that local research ethics boards formally accept this entry of de identified data.

Antiplatelet Therapy

ASA resistance (ISTH study proposal) - M. Rand/ M. Albisetti

A significant benefit of ASA has been demonstrated in the prevention of arterial thrombotic events in high-risk adult patients. Recurrent thromboembolic events have been reported in 5-45% of patients despite ASA therapy; this has been termed ASA 'resistance', but may actually reflect treatment failure. The failure of ASA to affect ASA-dependent laboratory tests has also been termed aspirin 'resistance'. The Working Party on ASA Resistance of the Platelet Physiology Subcommittee has concluded that a clinically meaningful definition of ASA 'resistance' needs to

be developed, based on data linking ASA-dependent laboratory tests to clinical outcomes in patients. Studies in children are required to explore ASA 'resistance'. In an ongoing prospective study of ~100 children with arterial ischemic stroke, 20% are aspirin 'resistant' based on laboratory testing. A prospective study in children following interventional cardiac catheterization is undergoing ethics approval, and several other centres with appropriate patient populations have been identified.

Recommendations: Encourage international participation in this cohort study to determine the percentage of children who are ASA resistant. Further studies are required to determine alternative anti platelet agents in ASA resistant children.

Predictors of Bleeding

Coagulation tests as predictors of Bleeding in CPB: New ways to predict bleeding /When should we test – G. Kenet/ N. Schlegel

Tonsillectomy and adenoidectomy are the most common surgical procedures performed in children. Despite the progress made in this type of surgery, the operative hemorrhagic risk factors are not clearly defined. However, the occurrence of either peri or post surgery hemorrhage is considered as potentially life threatening due to the anatomical location of the palatine tonsils and the adenoids. Hemorrhage is the most common complication of such a surgery. An estimated 2-3% of patients have hemorrhage and 1 of 40,000 patients die from hemorrhage. Bleeding may occur during surgery or after surgery either within the 24 hours (primary hemorrhage) or between day 2 to 10 (secondary hemorrhage). Pre-surgery physical examination and questioning for personal and familial bleeding history are recognized to be the most informative procedures. By contrast, in absence of controlled trials, there is no consensus of opinion about the practice of pre surgery haemostasis tests. The pediatric specifics: developmental haemostasis peculiarities, risks of coagulation activation due to difficult blood drawing, risks of artifactual results due to heparin contamination, enhance the poor positive predictive value for bleeding of the screening tests for platelet functions and the limitations of INR and aPTT. The inherited haemostasis disorders associated with bleeding risks, which are rare diseases (Von Willebrands disease being more common), are mostly diagnosed early in life, but some defects might be unknown at the time of the surgery. Taking into account the pros and cons, the most common attitude is to perform screening tests in the following situations: any child before walking age, positive personal and/or familial bleeding history, acquired disease with hemorrhagic risk, drugs associated with bleeding risk, family questioning not reliable, not relevant or not possible.

Official recommendations will be helpful from both the medical and legal points of view. The recommendations will facilitate a pre surgical estimate of the risk of bleeding and appropriate preventative therapies within the expert team (anesthesiologist, surgeon and hematologist). Platelet count and aPTT appear to be the most useful initial pre tonsillectomy and adenoidectomy tests to complete. If there are any concerns re peri surgical bleeding, Von Willebrands Disease testing should be completed pre surgery. Currently, there are no validated platelet function tests that allow a reliable assessment re peri surgical bleeding risk.

Recommendations: A subgroup lead by Gili Kenet and Nicole Schlegel will explore the institution of pre surgical questionnaires that indicate a potential peri surgical bleeding risk. The subgroup will liaise with Francesco Rodeghiero and the European Union re the validated and pre existing questionnaire for bleeding associated with Von Willebrands Disease. This established questionnaire may have potential application to tonsillectomy and adenoidectomy bleeding risk.

Cardiopulmonary Bypass (CPB) and Stroke: Update – A. Chan /P. Massicotte

Arterial ischemic stroke (AIS) is likely to be an important complication arising from cardiopulmonary bypass in children. The best estimated incidence of AIS at the present time is 0.4%. The three parameters that have been associated with an increase incidence of AIS are older age at the time of CPB, longer bypass time and lower pre-op activated partial thromboplastin time. Forty-eight percent of the patient with AIS had severe to moderate neurological deficit. However, large multicentre prospective studies are necessary to determine the incidence, risk factors and long term outcome of such complications. Optimization of anticoagulation therapy and cardiopulmonary bypass techniques, and development of neuroprotective agents are necessary in order to prevent the devastating long term complications associated with CPB, such as AIS.

Recommendations: The subcommittee has submitted a position paper to the SSC and awaits comments/approval. This position paper will facilitate properly designed incidence studies.

Thromboprophylaxis of mechanical heart valves: Point of Care Testing (ISTH position paper) – M. Bauman / F. Newall

Children with mechanical prosthetic heart valves require oral antithrombotic therapy using vitamin K antagonists. Monitoring vitamin K antagonists in children is difficult as they usually have complex underlying health problems, are on multiple medications and are often difficult to venesect. The cohort of children requiring primary thromboprophylaxis for the management of mechanical prosthetic heart valves is further challenging due to their lifelong need for thromboprophylaxis. This position paper will discuss the rationale for point-of-care capillary monitoring of vitamin K antagonists and provide an overview of POC monitoring. Clinical recommendations will be made regarding the use of POC testing generally, and use of this technology in home monitoring programs. POC INR monitoring, including home INR monitoring, in children has been demonstrated to be safe and efficient with the setting of dedicated paediatric anticoagulant clinics. Whether such monitoring remains safe and efficient when implemented within other models of care has not been determined. Implementation of strategies to reduce the risk associated with reduced reliability of POC INR results greater than 5.0 can optimize this management strategy. Consideration should be given to the education program upon which home INR monitoring programs are built.

Recommendations: The position paper is ready for comments/review by the subcommittee members. This will facilitate properly designed studies to determine safety and efficacy, quality of life and cost effectiveness of POC monitoring in children.

Risk factors for Venous Thrombosis/Thromboprophylaxis

Factor VIII, lipoprotein (a) and other risk factors in Thrombosis Recurrence in children. Update of Studies **U. Nowak Gottl/ M. Manco Johnson**

In children FVIII assays must have cut off values for abnormal which are dependent upon age and blood group. If FVIII is persistently increased, there is controversial data as to whether this is associated with an increased risk of VTE. Goldenberg et al show an increased risk of recurrence while Nowak Gottl et al demonstrate no increased risk of recurrence (unpublished data).

In children lipoprotein a cut off values for abnormal are age related. Increased lpa is associated with an increased risk of recurrent stroke. It is unclear whether recurrent VTE is associated with increased lpa.

Recommendations: More studies to determine the relationship of FVIII to the development of VTE in children are necessary.

Antiphospholipid Antibodies: Risk of Thrombosis in Children with APLA+: Status of manuscript (ISTH position paper) **C. Male**

Antiphospholipid antibodies (APLA) occur in children with a variety of conditions, most frequently following infections. However, APLA associated with thrombotic events (TE) are essentially limited to children with underlying autoimmune disease. The best evidence on the risk of TE associated with APLA comes from studies in children with systemic lupus erythematosus (SLE). Multiple laboratory tests for APLA are available but there are conflicting reports which test best predicts an increased risk of TE.

A recent cohort study of 58 consecutive children with SLE determined lupus anticoagulants (LA), anticardiolipin antibodies (ACLA), anti- b 2 -glycoprotein-I (anti- b 2 GPI), anti-prothrombin (anti-PT) in serial samples and prospectively (and retrospectively) assessed patients for symptomatic TE, confirmed by objective radiographic tests. Ten TE occurred in 7 patients (12%). Lupus anticoagulant showed the strongest association with TE since no LA-negative patient had TE. LA remained the only significant factor in multivariable analysis. Persistent ACLA, anti- b 2 GPI, and anti-PT were all significantly associated with TE. Considering all positive (persistent and transient) antibodies, the strength of association remained similar for LA and anti- b 2 GPI, while ACLA and anti-PT were no longer associated with TE. Positivity for multiple APLA subtypes showed substantially stronger associations with TE than for individual APLA subtypes because of improved specificity.

In conclusion, the criteria to best predict the risk of TE associated with APLA in children are: 1. underlying autoimmune disease, e.g. SLE; 2. persistent presence of APLA; 3. presence of LA, and 4. positivity for multiple APLA subtypes.

Recommendations: The risk of thrombosis in children with APLA+ will be submitted to the SSC for publication.

Open Prospective International Registry: Infants of mothers with APLA syndrome **M. H. Auroseau, Lachassinne E, Fain O, Biasini-Rebaioli C, Derenne S, Boinot C, Schlegel N, Avcin T, Le Toumelin P, Nicaise P, Faden D, Tincani A, Uzan M and Boffa MC.**

The aim of this register is to evaluate the correlation between maternal disease / treatments and the clinical events, neuro-developmental features and immunological status of the babies. The prevalence, type and kinetics of disappearance of antiphospholipid antibodies (APLA) in infants and children born to mothers with primary or secondary APS can be determined, according to Sapporo criteria. The potential effects of these antibodies will be evaluated in children until the age of 5. In 54 babies already included, we observed a higher prematurity rate than in the normal neonatal population. All types of APL antibodies were found in 39% of the neonates and in 5/54 neonates, new specificities of antibodies, different from maternal antibodies, were present. The time of disappearance of these antibodies is prolonged to 6-18 months. Furthermore, we observed 8 children, negative at birth who subsequently became positive. The registry is expected to recruit 300 neonates and mothers within the next 3 years.

To download the data base and to send the form please contact: philippe letoumelin@avc.ap-hop-paris.fr

Treatment and Prophylaxis of Thrombosis

Treatment of venous thrombosis - E. Chalmers/ H. Van Ommen

There are no new studies determining the safety and efficacy of medical therapy for venous thrombosis in infants and children. The differing treatment practices for venous thrombosis in infants and children were determined in an international survey (see below).

Recommendations: The results of the survey to be published will facilitate the design of treatment studies in infants and children with venous thrombosis.

Central Venous Lines: Thromboprophylaxis: Status of manuscript (ISTH position paper) **S. Revel-Vilk / L. Mitchell**

The two high risk groups with CVL related thrombosis that have been identified are children with ALL and children with congenital heart disease (CHD). Need summary

Recommendations: The recommendations for thromboprophylactic studies in these high risk groups will be submitted as a position paper to the SSC.

Report on Diagnosis and Treatment of DVT in children: Survey of the Pediatric Perinatal SSC (ISTH publication). **L. Bomgaars**

The Pediatric Perinatal subcommittee (30 members) was surveyed re the diagnosis and treatment of VTE in infants and children. There were 17 questions in the survey which was completed by 72% of the members (18 centres, 9 countries). The conclusions are :

1. LMWH as part of therapy in neonates is considered standard of care by all surveyed.
2. Objective testing schedule and duration of therapy is highly variable.
2. Thrombophilic work ups are more often performed in children as compared to neonates and most commonly included the measure of Protein C, S, Antithrombin, Factor V Leiden, and prothrombin 20210 defect.
3. Further RCTs are needed to define optimal therapy and evaluation in children.

Recommendations: The determination of international expert practice for the diagnosis and treatment of thrombosis in infants and children will facilitate the design of proper safety and efficacy studies. The results of this survey will be submitted as a position paper to the SSC.

Antiphospholipid Antibodies

Risk of thrombosis in children with APLA – C. Male

There is good evidence of a high risk of thrombosis in children with SLE and APLA. The association of APLA with TE found in pediatric cohorts are stronger than those found in adult studies. Few children with SLE who are negative for APLA develop TE. Lupus anticoagulant is a stronger predictor of the risk of TE than anticardiolipin antibodies, anti beta 2 glycoprotein antibodies and anti prothrombin antibodies.

In children without underlying SLE case reports describe associations of APLA and severe thrombotic complications (primary APLA syndrome). Currently, it is unknown what the risk of TE is in well children with APLA. Increased prevalence of APLA are found in children who suffered from stroke compared to controls. However, recent evidence suggests, in general, APLA presence is not associated with an increased risk of recurrent stroke.

Recommendations: The subcommittee recommends that the data on stroke and APLA in children be published in a Position paper with the recommendations that more studies are urgently needed in this area especially in primary prophylaxis of patients with APLA and SLE.

Perinatal/Pediatric Haemostasis

Chair: P. Massicotte, Canada

Past Chair: U. Nowak-Gottl, Germany

Co-chairs: G. Kenet, Israel; P. Matthew, USA; P. Monagle, Australia; W. Muntean, Austria; N. Schlegel, France

THROMBOSIS

A. CONGENITAL HEART DISEASE

1. Cardiopulmonary Bypass and Stroke: AKC Chan/P Massicotte

A discussion on the status of the ISTH position paper was presented.

2. Thromboprophylaxis of Mechanical Heart Valves: Point of Care testing M. Bauman/ F. Newall

An update about the ISTH position paper was discussed with the manuscript currently in preparation

3. Point of Care monitoring: Patient Education programs and outcomes.

M. Bauman/ F. Newall

Point of Care (POC) monitoring of anticoagulant therapy represents a potential solution to the challenge of safe and effective dosing of warfarin in children. Standardized, comprehensive, education provided preceding warfarin treatment and POC monitor use positively impacts reliability of results and improves outcomes for children requiring warfarin therapy. The implementation of a formalized focused education program results in excellent correlation between lab /POC INR result $r^2 = 0.96$, increased time in INR therapeutic range (TTR) (84%) $p = 0.04$, increased patient knowledge $p < 0.0001$, and improved adherence and no thrombotic or bleeding results. POC INR monitors are a safe and effective alternative for monitoring INR in children who underwent a standardized comprehensive education program, preceding patient self testing with a POC INR monitor. Long term knowledge retention and its influence on safety and efficacy will be evaluated.

Recommendations : The education package can be provided in English and French (when translated) to those who are interested by contacting marybauman@cha.ab.ca .

B. RISK FACTORS FOR THROMBOSIS

1. Recurrent Pediatric Stroke and risk factors **U. Nowak Gottl/ G. deVeber:**

Data on recurrent stroke from pooled international databases held at the hospital for sick kids, Toronto , University of Munster and Great Ormond Street hospital, UK were presented. The effects of thrombophilic risk factors for the risk of recurrent stroke was evaluated. Data were available from 678 patients (age range: 1 month to 21 years) followed for a median of 36 months. Recurrence rates were significantly higher among patients with cardio vascular diseases

and increased lipoprotein (a) levels. The presence of any prothrombotic risk factor doubled the risk for recurrence after adjustment for presence of cardiovascular disease, whereas the use of either antiplatelet or anticoagulant therapy significantly reduced it.

Recommendations: Due to the paucity of information regarding the risk of recurrent stroke in children, pooled international data collection and further collaborative studies were strongly encouraged.

2. Antiphospholipid Antibodies: Risk of thrombosis in children with APLA+: Results of the Israeli experience **G. Kenet:**

There are only few small case series regarding the issue of primary APS in the pediatric population. In Israel, a cohort of 28 patients with APS was prospectively followed for a median of 6 years. Patients were assessed for presence of any other thrombophilic risk factors and any recurrent thrombosis. The commonest presenting symptoms were thrombotic, with a small subgroup presenting with perinatal stroke. Among laboratory markers of APS, LAC prevailed. During follow up, 5 females developed SLE, 7 patients suffered recurrent thrombosis that was not associated with presence of thrombophilia, and the recurrences were inversely related to anticoagulant therapy administration. The subgroup presenting with perinatal stroke and APL antibodies had a monophasic disease with no recurrences despite lack of anticoagulant therapy. Unique features of pediatric APS and the need for proper diagnosis and early anticoagulant therapy were discussed.

Recommendations : The committee suggested a potential future joint session with the APL subcommittee to discuss diagnostic criteria for pediatric patients and guidelines for therapy. Pediatric Hematologists were encouraged to join the European APLA registry, collecting data about infants born to mothers with APS. To receive more information about the registry, contact Nicole Schlegel at schlegel@wanadoo.fr

3. Evidence that Tissue Factor Is the Driving Force in Childhood HUS, with Direct Implications for Therapy and Clinical Studies **E Grabowski**

Up regulation of tissue factor activity is seen on TNF α activated human glomerular endothelial cells exposed to shiga toxin on proximal tubular cells exposed to this toxin and on sections of kidney from rabbits given this toxin orally. In the last case, platelet adhesion/aggregation on the sections is tissue factor driven, as shown by full inhibition of the increase seen with shiga toxin when sections are first incubated with a monoclonal antibody directed against human rabbit factor.

These animal studies suggest that a clinical/preclinical trial to evaluate the role of the tissue factor pathway in the childhood hemolytic uremic syndrome (HUS) is warranted. The clinical/preclinical trial would also evaluate the role of site inactivated factor VIIa in blocking this pathway and suggesting a novel therapy for the syndrome.

Recommendations : Samples of blood and urine from patients in the acute phase of childhood HUS are required to be tested in the in vitro cell culture systems. Any interested investigators should contact Dr Eric Grabowski at eric@MGM.harvard.edu

C. TREATMENT & PROPHYLAXIS OF THROMBOSIS

1. New Anticoagulants in children. **G. Young**

Low molecular weight heparins have overcome some of the limitations of unfractionated heparin yet, they can not inactivate clot bound thrombin, have a long half life and do not have a specific antidote. In adults, several new anticoagulants have been licensed in recent years to prevent and treat a variety of thromboembolic complications. These agents have superior pharmacologic properties to heparin and some have shown a dramatic reduction in the risk for bleeding without compromising efficacy. These agents have properties which make them particularly attractive for evaluation in children. Data was presented on the results of 2 single centre pilot dose finding and pharmacokinetic studies using 1. bivalirudin in infants with thrombosis and 2. argatroban in children who have heparin induced thrombocytopenia (HIT). The data for dosing and safety of both agents suggests safety and efficacy in infants and children.

Recommendations : Properly designed studies including pharmacokinetic and pharmacodynamic studies are required with the new anticoagulant agents in children to determine safety and efficacy.

2. Central venous lines: thromboprophylaxis: ISTH position paper **S. Revel Vilk/L. Mitchell**: An update of the manuscript status was presented; manuscript is currently in preparation.

3. Report on Diagnosis and Treatment of DVT: Survey of SSC.(Status of manuscript) **L. Bomgaars/ P. Massicotte**: An update of the manuscript status was presented; manuscript is in preparation.

BLEEDING

A. TREATMENT OF BLEEDING

1. FVIIa use in non haemophilic children: International Registry update. (ISTH study) **P. Mathew/J. Blatny**:

Presently, n= 30 patients have been entered into the registry. Committee members were asked to increase their level of awareness and report all off-label use in pediatric patients into this registry.

2. New study : FVIIa in IVH in premature infants **P. Mathew**: The rationale for this study was presented and a draft outline was discussed.

3. Acquired Purpura Fulminans: The Argentinian Data **M. Bonduel**

Sixty-three children with clinical diagnosis of APF related to suspected infectious diseases were retrospectively evaluated in Argentina . *Neisseria meningitidis* was the microorganism most frequently isolated. All patients had signs of DIC, and most of them required mechanical ventilation and inotropic support.

On admission, plasma samples of 31 patients with APF associated with different infections were evaluated. There was a significant difference in PC, PS and AT levels between survivors and non- survivors. PC was significantly lower than AT or PS. In varicella associated APF (n=6) severe deficiencies of free and total PS were detected.

The patients were treated with fresh frozen plasma, protein C concentrates (n=9), or recombinant APC concentrate (n=1). No bleeding events were observed. Despite the therapies used, high percentages of mortality and severe morbidity, in some groups of patients, were found.

Recommendations : More data should be collected in APF in children to elucidate possible therapeutic measures which should ultimately be tested in clinical studies.

B. ANTIPLATELET THERAPY

1. ASA resistance (ISTH study update) **M Rand/M Albisetti**

The clinical efficacy and dosing of ASA in children have not been well studied. The Working Party of ASA ‘Resistance’ of the Platelet Physiology Subcommittee of the SSC has concluded that: 1) a clinically meaningful definition of ASA ‘resistance’ needs to be developed, based on data linking ASA-dependent laboratory tests to clinical outcomes in patients; and 2) the correct treatment, if any, of ASA ‘resistance’ is unknown. (Michelson et al., *J Thromb Haemost* 2005;3;1309).

Studies in Canada, the USA and Switzerland are now ongoing to explore ASA ‘resistance’ in children; in one of these, a prospective study of ~120 children with arterial ischemic stroke, 20% are ASA ‘resistant’ based on laboratory testing. Several other centres with appropriate patient populations have been identified.

Recommendations : To continue to work with the Platelet Subcommittee in this area. To complete studies in children to provide data to clarify the definition and clinical relevance of ASA resistance in children

C. PREDICTORS OF BLEEDING

1. Tests used to predict bleeding in children before adenoidectomy and tonsillectomy: ISTH questionnaire results **G. Kenet/ N. Schlegel**

Due to the lack of information there is currently no consensus regarding pre-operative screening questionnaire and screening tests for bleeding in young children undergoing various surgeries. Prior to SSC meeting a pediatric bleeding proposed questionnaire has been submitted to committee members for approval and comments. Following the correspondence, it has been

suggested to use the VW questionnaire (with some pediatric modifications) as baseline screening for any child and for parents of younger children as well. The score of this questionnaire should be added to the score of surgical procedure (differentiating high and low risk surgeries, with regard to bleeding potential) and the score of abnormal laboratory screening tests (to be obtained for every child with high-risk bleeding history or high-risk surgery as well as selected cases upon clinical experts definition) in order to stratify the risk of bleeding for patients undergoing various surgical procedures.

Recommendations: A sub group led by G. Kenet/ N. Schlegel will work upon further definitions of bleeding score. The committee members have agreed to prospectively collect data of patients referred for peri-operative screening according to questionnaire and score suggested. Contact gili.kenet@sheba.health.gov.il if you are interested in participating in the sub group.

2. Pre op PFA-100 screening in 500 children **W. Muntean**

Peri-operative screening of 500 children referred for Hematology consultation due to potential high-risk bleeding history was performed by using 2 assays: PTT and PFA-100. Neither prolonged PTT, nor prolonged closure time of PFA-100 were associated with operative bleeding in this group despite a number of children with prolonged PTTs and closure times. This may have resulted due to limitations of both tests, as well as non-reliability of the screening questionnaire as administered by non-expert physicians.

Recommendations: To try to further define the risk for bleeding through questionnaires and laboratory predictors as suggested above.

Perinatal/Pediatric Hemostasis

Chair: G. Kenet (Israel)

Co-Chairs: J. Journeycake (USA), P. Massicotte (Canada), P. Mathew(USA), P. Monagle (Australia), W. Muntean (Austria), N. Schlegel (France)

A: Pediatric thrombosis- chairs: P Massicote, U Nowak-Gottl

1. Recurrence of venous thromboembolism in pediatric population: **A Chan**

Recurrence is a major end-point in VTE studies, yet there are few evidence based data about this issue in pediatric patients. Comparison between neonates and children was emphasized, focusing on outcome studies available for neonatal RVT. Neonates exhibit a very low risk of reported recurrence as compared to older children. Spontaneous VTE, prothrombotic risk factors and presence of co-morbid states have been shown to increase recurrence rate, whereas D-Dimer elevation and higher factor VIII have been associated with adverse outcome of pediatric VTE. The duration as well as intensity of anticoagulant treatment to prevent recurrence in children still need to be elucidated.

Recommendation: More data should be collected on recurrence rate among neonates and children, including impact of anticoagulation therapy and presence of risk factors.

2. Factors affecting recurrence of stroke and CSVT in pediatric patient: **U Nowak-Gottl**

Data on recurrent stroke and Cerebral Sinus vein thrombosis (CSVT) from pooled international databases held at the hospital for sick kids, Toronto, University of Munster, Tel Hashomer hospital- Israel, and Great Ormond Street hospital, UK were presented. The impact of thrombophilic risk factors upon risk of recurrent stroke was evaluated. Data were available from 678 stroke patients (age range: 1 month to 21 years) followed for a median of 36 months. Recurrence rates were significantly higher among patients with cardiovascular diseases and increased lipoprotein(a) levels. The presence of any prothrombotic risk factor doubled the risk for recurrence after adjustment for presence of cardiovascular disease, whereas the use of either antiplatelet or anticoagulant therapy significantly reduced it.

For CSVT recurrence, 396 children were prospectively followed. Age at onset (>2 years, non-administration of antipagulants, persistent venous occlusion and presence of FIIG20210A variant were independently associated with higher recurrence risk.

Recommendations: Due to the paucity of information regarding the risk of recurrent stroke in children, pooled international data collection and further collaborative studies are strongly encouraged

B: Therapy of pediatric Thrombosis. Chairs: W Muntean, M Bonduel

1. Heparin therapy in children: **P Monagle**

The differences between children and adults treated with unfractionated Heparin (UFH) regarding bleeding tendency, monitoring tests, the mechanism of action and half life of UFH were discussed.

Recommendations: Further specific and targeted studies of pharmacokinetics, dosing schedules and monitoring strategies in children should be done .A position paper, which recommends the desired strategies for assessing UFH therapy in neonates and children has been suggested.

2. TPA in pediatric stroke: **K Leofond**

TPA is being given for childhood stroke according the adult guidelines with small deviation, despite the differences in physiologic and fibrinolytic systems of children as compared to adults. Preliminary data of TPA therapy in pediatric patients with stroke were presented.

Due to minimal information concerning the safety and appropriate dosing of tPA in childhood stroke, a multi-centre cohort safety and dose-finding study has been designed to assess tPA in childhood stroke by the International Pediatric Stroke Study (IPSS).

Recommendation: International collaboration is encouraged.

3. New Anticoagulants in children: **G Young**

Newer anticoagulant agents are available and licensed, with potential advantages over heparin, low molecular weight heparin and warfarin. Summary of bivalirudin pilot study and preliminary data on argatroban study in children with thrombosis were presented. Laboratory studies utilizing thromboelastography with five different anticoagulants and their potential in-vitro reversibility by rFVIIa were discussed.

Recommendation : Randomized controlled clinical trials are recommended since the use of anticoagulation recently increased in children despite lack of information.

4. Thrombolysis in pediatric DVT-new study proposal: **M Manco Johnson**

A proposal for a new international multicenter study has been made, based upon better outcome with lower rate of post-phlebotic syndrome in children reported treated with systemic thrombolysis as compared to standard anticoagulant therapy.

Recommendation : Studies are required to assess the role of thrombolytics (either systemic or regional vs heparin alone) in pediatric VTE.

C: Pediatric bleeding –chairs: N Schlegel, M Rand

1. Towards a standard bleeding score in pediatric patients: **M Rand**

Bleeding history evaluation in children is often difficult and has been challenged before. A specific adjusted bleeding questionnaires has been validated in Sick-kids hospital, Toronto.

Pediatric-specific bleeding questionnaire based on the ISTH Bleeding questionnaire for the diagnosis of Type 1 von Willebrand Disease (VWD) was applied in collaboration with colleagues in: Kingston, Canada; Vicenza, Italy and Oakland, USA.

Recommendation: Use of standard bleeding questionnaires should be practiced, leading to better diagnosis and treatment for children with bleeding disorders

2. Bleeding score and questionnaire adopted for children: **N Schlegel**

The feasibility and efficacy of questionnaire and bleeding score in neonates, infants and children who were scheduled to undergo various surgeries, was presented.

A proposal for use of bleeding score composed of combined questionnaire results, lab tests and surgical bleeding risk assessment was made.

Recommendation: Collaborative international data collection of bleeding score results and outcome is proposed

3. Experience with VW questionnaire in pediatric patients: **C Bidingmayer**

A study that evaluated peri-operative PTT screening was discussed. Retrospective chart analysis of 492 consecutive patients (age 1-17 yrs., Median 5), referred for hemostatic assessment, after evaluation of PTT screening and history, for standardized laboratory workup was presented. Only in 35% of patients prolonged PTT was confirmed, 2.4% suffered from significant bleeding disorder (BD). The positive predictive value (PPV) to detect BD for prolonged PTT in combination with positive bleeding history was higher.

Recommendation : Since PTT screening yields many false positive results, an effort of the ISTH Pediatric SSC to validate standard questionnaires and scores for evaluation of bleeding risk in children undergoing surgery is urgently required.

D. Perinatal Hemostasis – chair: J Journeycake

Neonatal IVH : past, present and future perspectives : **P Mathew**

Neonatal IVH is responsible for many adverse sequelae including post hemorrhagic hydrocephalus, cerebral palsy and death. Reducing the risk of progression to higher grades of IVH in VLBW infants and thereby reducing adverse long term outcome by proper intervention therapy should be attempted.

A study to investigate the natural history of early germinal matrix-(GM-IVH) in very low birth weight (VLBW) infants and to evaluate the safety of using rFVIIa in preterm infants was presented

Recommendation: A prospective study of the natural history of neonatal IVH has been proposed and submitted for funding.

Perinatal/Pediatric Hemostasis

3 July 2008
Vienna, Austria

Chair: *Gili Kenet, Israel*

Co-Chairs: *Janna M. Journeycake, USA; Prasad Mathew, USA; Paul Monagle, Australia; Wolfgang Muntean, Austria; Ulrike Nowak-Gottl, Germany; Nicole Schlegel, France*

DRAFT

Thrombosis, risk factors and recurrence Chairs: J Journeycake, USA, U Nowak-Gottl, Germany

1. **Meta-analysis of risk factors for recurrent DVT - Ulrike Nowak Gottl, Germany**

Recurrence is a major end-point in VTE studies, yet there are few evidence based data about this issue in pediatric patients. The aim of the study was to objectively estimate the impact of inherited thrombophilia (IT) on early onset of venous thromboembolism (VTE) and recurrence in children. A systematic meta-analysis was conducted, yielding data of nearly 3000 pediatric patients and 2000 healthy controls. An association between the IT traits and VTE onset was found. Association with recurrent VTE was found for protein S-, antithrombin-deficiency, factor II variant and combined ITs. Notably, in these studies > 70% of patients had at least one clinical risk factor. This meta-analysis gives evidence that the detection of IT is clinically meaningful in children with VTE and underlines the importance of a pediatric thrombophilia screening program.

Recommendation: Further studies are required to evaluate if risk stratification for anticoagulant therapy, based on underlying thrombophilic traits, will reduce recurrent VTE in pediatric population.

2. **FIIG20210A and FVL as risk factors for recurrent thrombosis in children- Guy Young, USA**

Factor V Leiden and the FIIG20210A are the most prevalent genetic thrombophilias, however, their role in VTE recurrence in children is unclear. In a multicenter international cohort the rate of VTE recurrence and the time to recurrence in relation to FII, FV and other clinical variables was determined, in consecutively enrolled VTE - patients aged newborn to <18 years carrying the FII variant (n=64) or the FV mutation (n=194). Patients were followed for a median of 58 months. Multivariate analysis showed that presence of the FII mutation, persistence of thrombus at 3-6 months and increasing age were associated with an increased rate of VTE recurrence.

Recommendation: Thrombophilia screening in pediatric VTE patients is recommended, since presence of FIIG20210A may predict higher risk of thrombosis recurrence.

3. **CVL thrombosis, results of a multicenter study -Shoshana Revel-Vilk, Israel**

Central venous lines (CVL) are an essential part in the treatment of children with cancer. In order to evaluate the risk factors for CVL complications, a multi-center Israeli registry database on children with cancer and CVL was established and 263 children with 415 CVL's were enrolled and followed for 18 months. Only nine clinical DVT's evolved, however over 90 CVL obstructions occurred and were associated with line infection.

Recommendation: Uniform guidelines for all pediatric oncology centers will improve the supportive care of children with cancer and are essential for prevention of infections, line occlusions and thrombotic complications.

4. **APLS with thrombosis in pediatric patients- Mariana Bonduel, Argentina**

This study analyzed the clinical and laboratory manifestations in a pediatric Argentinian APS cohort. APS in children had unique features. LA was the most frequent APLA detected in this pediatric cohort with DVT. Thrombosis related to catheters was frequently detected and may be discussed as a clinical criteria for APS in children. Thrombotic recurrence and death attributable to thrombosis were seen in patients with the co-existence of LA and severe underlying diseases.

Recommendation: Guidelines for definition of pediatric APLA and the management required to decrease thrombosis recurrence in pediatric APS patients should be discussed and validated by further studies. Potential collaboration with Lupus Anticoagulant SSC may be beneficial for future definitions.

Thrombosis complications and therapy. Chairs: G Kenet, Israel, N Schlegel, France

1. Post thrombotic syndrom (PTS) in children - Anjali Sharathkumar , USA

PTS is the long-term complication of pediatric VTE, reported in the literature between 9% and 70%. Clinical characteristics of early and late complications of children with VTEs who were managed by Pediatric coagulation service at University of Michigan (2005-2007) were critically reviewed. Based on the symptoms, an expanded PTS assessment scale (EPTSAS) for children was developed and suggested as tool to assess PTS among pediatric patients.

Recommendation: Clinical PTS scoring system should be applied in further international multicenter pediatric VTE studies. A pediatric SSC working group should try to establish and validate different PTS scores- see also below.

2. PTS-Canadian registry results and discussion: Leonardo bradao, Canada

A retrospective pediatric cohort treated and followed at the Hospital for Sick Children from June 1996 to July 2007 was reviewed for PTS presence following upper arm DVT (UADV). PTS incidence was approximately 40% with a trend towards increased prevalence and severity in primary UEDVT in children. Long-term follow up showed higher symptom resolution in UEDVT-related PTS, thus its significance deserves further attention.

Recommendation: Potential collaboration with the anti-coagulation control SSC for better definitions of pediatric PTS is suggested and physicians are invited to contact either L Brandao, A Chan or A Sharathkumar for further details.

3. Dosing and monitoring heparin in children during cardiac catheterization - results from a randomized trial (HEARTCAT study). A.Hanslik, C. Male, Vienna, Austria.

Monitoring unfractionated heparin (UFH) in children is problematic because of variable dose-response. A comparison between high dose (100 u/kg) and low dose (50 u/kg) UFH for prevention of thrombosis during elective cardiac catheterization was conducted. Vascular complications were less frequent than anticipated. High and moderately high doses of UFH were well discriminated using aXa, less favourable correlations were noted with application of TG, ACT and APTT.

Recommendation: Further specific and targeted studies of pharmacokinetics, dosing schedules, and monitoring strategies in children should be preformed. Collaborative international data collection will be established by C Male, P Monagle and L Brandao (see below) to evaluate the best monitoring (aXa vs APTT or other) in pediatric patients treated with UFH.

4. Heparin dosing and monitoring in infants- Leonardo Brandao, Canada

The recommended UFH dose for infants is significantly higher than patients > 1 year of age. Data was collected from a cohort of infants < 6 months of age treated with UFH, followed at Thrombosis Service at Sickkids®, Toronto, from 2004-2006. The safety, efficacy and dosing was evaluated. Most infants required

higher than recommended UFH dosing in order to achieve therapeutic anti-Xa levels. The incidence of major bleeding was 11%.

Recommendation: Further studies regarding dosing and safety are recommended (see above).

Heparin therapy, Bleeding risk Chairs: W Muntean, Austria, M Rand, Canada

1. Stratification of therapy risk with anticoagulants in neonates- **Anthony K Chan, Canada**

The safety and efficacy of anticoagulant treatment in neonates with portal vein thrombosis, renal vein thrombosis and cerebral sinus vein thrombosis was presented with about 6% major bleeding and up to 72% efficacy (though high rate of specific late sequels) in previous studies. Multidisciplinary international multicenter studies are suggested in order to stratify age-adjusted therapy according to pre-clinical condition.

Recommendation: International data collection (registry/ further studies) are suggested

2. HIT studies in pediatric patients- Eric Grabowski, USA

Identification of Heparin-associated thrombocytopenia (HIT) in infants and older children is different from that for young and older adults. An upcoming study was presented: comparison of confirmed/suspected HIT cases with controls in order to better understand HIT classification in children. Further studies with emphasize on safety and efficacy doses of newer anticoagulants in small children are encouraged.

Recommendation: Modification of Warkentin criteria and positive ELISA (with adult “cut off” OD values) for pediatric patients is suggested and should be tested by pediatric HIT studies, for further details please contact speaker.

3. Bleeding questionnaire for detection of mild VW in children- W Muntean, Austria

Bleeding questionnaires in order to evaluate risk for bleeding post surgery may not be sensitive enough, since rate of pediatric post surgery bleeding is usually low(1-3 %). A comparison was conducted, using questionnaires, between 88 children in whom a hemorrhagic disorder was ruled out by rigorous laboratory investigation, to a group of 38 children with mild von Willebrand disease (vWD). The detailed questionnaire yielded good results to exclude a hemostatic disorder, but was not a sensitive tool to identify such a disorder.

Recommendation: Use of standardized bleeding questionnaires should be encouraged; however, more sensitive tools for evaluation of bleeding disorders are required. The joint working group of our SSC with the VW-SSC is currently discussing standardization of bleeding questionnaires.

4. New bleeding questionnaire and bleeding risk score- N Schlegel, France

The feasibility and efficacy of the questionnaire and bleeding score in neonates, infants and children who were scheduled to undergo various surgeries was presented. A proposal for use of bleeding score composed of results of bleeding questionnaire, lab evaluation and surgical risk of bleeding was made.

Recommendation: Collaborative international data collection of bleeding score results and outcome is proposed, please contact speaker.

Submitted by G. Kenet